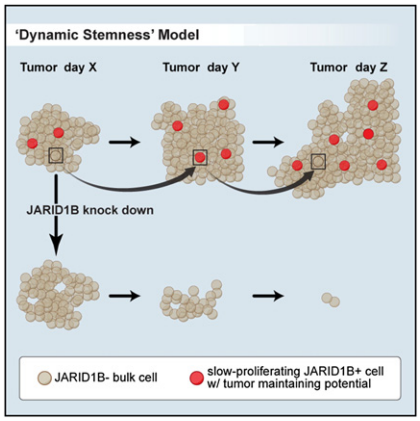
In This Issue

Cell

Cancer Stem Cells as a Moving Target

PAGE 583

Malignant melanomas are highly heterogeneous tumors, but whether all cells or only a subtype have cancer stem cell potential is not clear. Using the histone demethylase JARID1B as a biomarker, Roesch et al. characterize a small subpopulation of slow-proliferating melanoma cells that is essential for continuous tumor growth. Expression of JARID1B is dynamically regulated, as cells can lose or gain expression. The authors therefore propose that tumor maintenance is a dynamic process and is mediated by a temporarily distinct subpopulation of cells, which do not follow a hierarchical cancer stem cell model.



Transcription Factor Clears Replication Roadblocks

PAGE 595

Replication and transcription are two fundamental cellular processes that act simultaneously on DNA. Looking at the interplay between the two, Tehranchi et al. find that DksA, a nutrient-responsive transcription factor, ensures replication completion in *E. coli* by removing transcription roadblocks. This role for DksA is independent of its transcription initiation activity, but instead requires a previously uncharacterized elongation activity. Therefore, transcription elongation factors can alleviate conflicts between replication and transcription by protecting replication fork progression and DNA integrity.

The SAGA of Deubiquitinase Activation

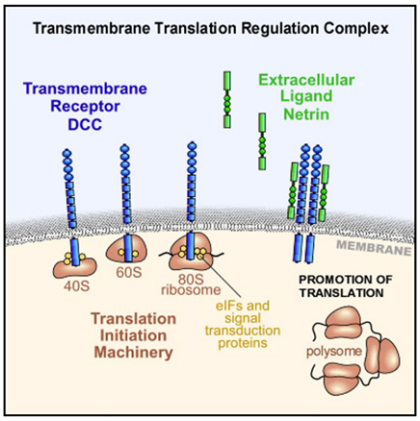
PAGE 606

Deubiquitinating enzymes (DUBs) regulate key cellular pathways by cleaving ubiquitin from target proteins. The histone deubiquitinase Ubp8 is embedded within SAGA, a large transcription complex. How Ubp8 and other multisubunit DUBs are controlled by associated proteins is not understood. With a combination of structural and functional analyses, Köhler et al. now reveal how cofactors can regulate DUB activity allosterically and show that in the SAGA context three cofactors play highly specialized roles in DUB assembly and activation.

Neurons Burn through MicroRNAs

PAGE 618

MicroRNAs (miRNAs) are key posttranscriptional regulators of gene expression, but comparatively little is known about how they are regulated. Krol et al. show that miRNAs turn over rapidly in neurons. Unexpectedly, the rate of degradation can be tuned in response to changes in light in retinal neurons and to activity or inhibition in other neuronal populations. Hence, miRNA metabolism in neurons is higher than that in most other cells types and is linked to neuronal activity.



Taking Translation to the Membrane

PAGE 632

How is spatial precision of localized protein synthesis achieved when extracellular signals regulate translation? Here, Tcherkezian et al. find that a cell-surface transmembrane receptor, DCC, forms a complex with the translation machinery, including initiation factors and ribosomes. In response to the extracellular ligand netrin, DCC promotes translation. The results suggest that extracellular regulation of translation could be broadly based on a transmembrane translation regulation particle.

Peroxisomes Join Antiviral Force

PAGE 668

The ability to detect viruses in the cytosol of mammalian cells depends on RIG-I-like receptors (RLRs) that induce antiviral responses to fight infection. MAVS, an adaptor protein found on mitochondria, mediates RLR signaling and the subsequent interferon-dependent antiviral response. Dixit et al. now show that MAVS is also located on peroxisomes. Interestingly, RLR-mediated activation of peroxisomal MAVS induces antiviral gene expression independently of type I interferons. These results establish peroxisomes as an important site of antiviral signal transduction.

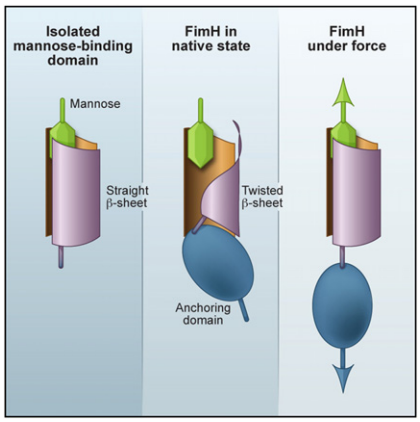
Phage Get Out the Vote

PAGE 682

When cell-fate decisions are examined at single-cell resolution, they often appear imprecise, or noisy. This phenomenon is usually attributed to randomness in chemical reactions in the cell. Zeng et al. use the classical lysis/lysogeny decision in phage lambda infection to demonstrate how the observed single-cell noise can be explained by a cascade of decisions occurring at the subcellular level. The authors show that individual viruses each "make decisions" that are accurately integrated in a cell-wide "vote," resulting in a cellular phonotype that appears to be much noisier than it really is.

A Sweet Catch and Release

PAGE 645

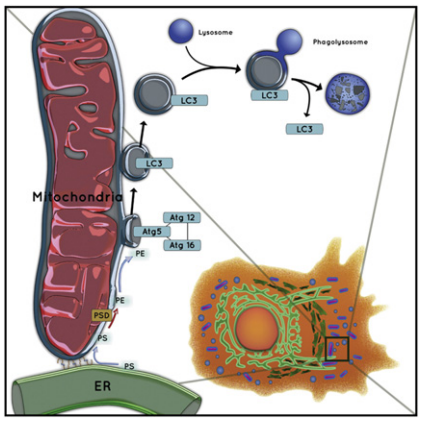


The *E. coli* adhesive protein, FimH, binds to mannosylated surfaces via a catch bond that becomes stronger with increased mechanical force. Le Trong et al. provide structural insight into how this catch bond works. They find that the FimH anchoring domain interacts with the mannose-binding domain and causes a twist in its β sandwich fold. Binding to the surface and the application force releases this autoinhibitory interaction and lets the binding domain enfold its sugar substrate. β sandwich proteins are thought to be rigid structures, but these results highlight that they can undergo allosteric twisting and subsequent untwisting under tension.

The Smell of Fear

PAGE 692

Mice detect unknown cues from predator species that warn of danger. Here, Papes et al. identify proteins from cats and rats that are sufficient to generate innate fear-like behavior in mice by activating vomeronasal (VNO) sensory neurons. The VNO is known for its role in detecting pheromones, chemicals that communicate information within a species. Thus, the findings indicate that in addition to detecting intraspecies social cues, the mouse VNO evolved to pick up on signals from other species.



Autophagosomes Starve for Mitochondrial Membranes

PAGE 656

During starvation, eukaryotic cells induce autophagy whereby autophagosomes trap cytosol en masse, fuse with lysosomes, and then release catabolites to fuel critical processes. How autophagosomes form and the origins of their membrane are long-standing questions. Using live-cell imaging, Hailey et al. demonstrate that the outer mitochondrial membrane participates in autophagosome biogenesis. This involvement is specific to starvation, suggesting that induction conditions dictate what membranes give rise to autophagosomes.

Hear Here!

PAGE 704

Inner-ear hair cells mediate hearing and balance. Oshima et al. demonstrate the in vitro-differentiation of embryonic stem (ESCs) and induced pluripotent stem (iPSCs) cells into otic progenitor cells that generate clusters of cells with typical sensory hair cell cytoarchitecture. Mechanical stimulation of the hair bundle-like protrusions of ESC- and iPSC-derived hair cell-like cells elicited currents that were highly reminiscent of immature hair cell transduction currents. In vitro generation of sensory hair cells has implications for the development of novel treatments for hearing loss and allows production of these scarce cells for molecular studies.

Secreted Senescence Factor Revisited

PAGE 717

The oncogenic mutation B-RAFV600E is common in both melanomas and benign nevi, moles. In nevi, aberrant proliferation of melanocytes is inhibited by senescence. A recent study identified IGFBP7 as the secreted protein mediating melanocyte senescence. In this issue, Scurr et al. reassess the role of IGFBP7 in senescence. They find no correlation between B-RAF mutational status and IGFBP7 expression and demonstrate that B-RAFV600E induces senescence irrespective of IGFBP7, indicating that IGFBP7 is dispensable for B-RAFV600E-induced senescence in human melanocytes.